Alpha-synuclein delays mitophagy and targeting Miro rescues neuron loss in Parkinson's models.

Journal: Acta Neuropathol

Publication Year: 2018

Authors: Atossa Shaltouki, Chung-Han Hsieh, Min Joo Kim, Xinnan Wang

PubMed link: 29923074

Funding Grants: Misregulated Mitophagy in Parkinsonian Neurodegeneration

Public Summary:
Alpha-synuclein is a component of Lewy bodies, the pathological hallmark of Parkinson's disease (PD), and is also mutated in familial PD. Here, by extensively analyzing PD patient brains and neurons, and fly models, we show that alpha-synuclein accumulation results in upregulation of Miro protein levels. Miro is a motor/adaptor on the outer mitochondrial membrane that mediates mitochondrial motility, and is removed from damaged mitochondria to facilitate mitochondrial clearance via mitophagy. PD patient neurons abnormally accumulate Miro on the mitochondrial surface leading to delayed mitophagy. Partial reduction of Miro rescues mitophagy phenotypes and neurodegeneration in human neurons and flies. Upregulation of Miro by alpha-synuclein requires an interaction via the N-terminus of alpha-synuclein. Our results highlight the importance of mitochondria-associated alpha-synuclein in human disease, and present Miro as a novel therapeutic target.

Scientific Abstract:
Alpha-synuclein is a component of Lewy bodies, the pathological hallmark of Parkinson's disease (PD), and is also mutated in familial PD. Here, by extensively analyzing PD patient brains and neurons, and fly models, we show that alpha-synuclein accumulation results in upregulation of Miro protein levels. Miro is a motor/adaptor on the outer mitochondrial membrane that mediates mitochondrial motility, and is removed from damaged mitochondria to facilitate mitochondrial clearance via mitophagy. PD patient neurons abnormally accumulate Miro on the mitochondrial surface leading to delayed mitophagy. Partial reduction of Miro rescues mitophagy phenotypes and neurodegeneration in human neurons and flies. Upregulation of Miro by alpha-synuclein requires an interaction via the N-terminus of alpha-synuclein. Our results highlight the importance of mitochondria-associated alpha-synuclein in human disease, and present Miro as a novel therapeutic target.